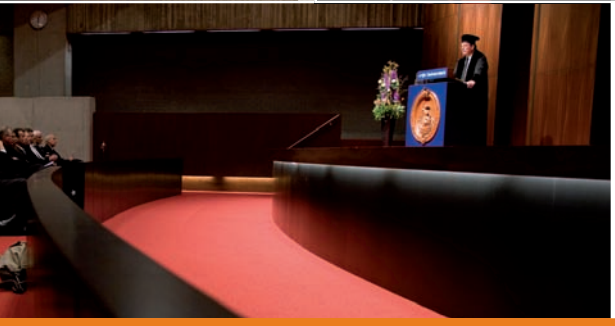
In praise of nutrients

Katan, M.B.

2011

In praise of nutrients

prof.dr. Martijn B. Katan - Faculteit der Aard- en Levenswetenschappen



vrije Universiteit *amsterdam*

In praise of nutrients

prof.dr. Martijn B. Katan

Rede uitgesproken ter gelegenheid van zijn afscheid als hoogleraar Voedingsleer aan de faculteit der Aard- en Levenswetenschappen van de Vrije Universiteit Amsterdam op 28 januari 2011.

vrije Universiteit *amsterdam*

Voor Emma

Mr. Rector, Ladies and Gentlemen,

The American journalist Michael Pollan has said *'Nutrition science is […] a flawed science that knows much less than it cares to admit'*.[1] Nutrition scientists are familiar with such denunciations of their field, but there are serious scholars who share Pollan's concern.[2,3] Often, yesterday's miracle food turns out to be not so great today. Think of low-fat high-carbohydrate diets and obesity, beta-carotene and cancer, or antioxidants and heart disease. All turned out not to work; beta-carotene even increased cancer rates. How could this happen? And how can we create nutrition knowledge that will stand the test of time?

Vitamins and the power of reductionist science

Nutrition became a science through the discovery of the vitamins. The approach there was strictly reductionist. Diseases like scurvy, beri-beri and rickets were traced back to a single substance in foods which in small amounts prevented or cured the disease. I myself became involved in nutrition through vitamin A and its effects on children's eyes. I am a physical chemist and biochemist by training,[4-11] and I strayed into nutrition because of a Chinese doctor. Almost 40 years ago doctor The Sie Po, the director of Saint Elisabeth hospital in Medan, wrote a letter to his Alma Mater, the University of Amsterdam. He was looking for help to start up a department of biochemistry at the Medical School of the University of Northern Sumatra. Prof. Piet Borst responded, and helped him and his colleagues to set up teaching and research. That research dealt with vitamin A deficiency and blindness in children.

At the time, I was a Ph.D. student in Piet Borst's laboratory, where I studied the biogenesis of mitochondria in yeast. When help was needed to set up an assay for vitamin A binding protein for the Medan project, I volunteered. The idea that my biochemistry skills might keep children from going blind was irresistible. Thus started my journey into nutrition.

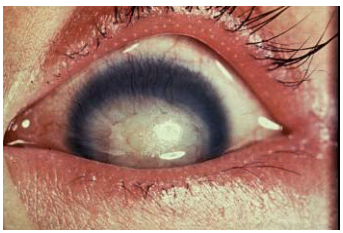


Figure 1. Blindness caused by vitamin A deficiency

Xerophthalmia is a classic vitamin deficiency disease. Vitamin A is needed in the retina to convert light into nerve pulses, but also for the integrity of epithelial membranes, including those that cover the eye. In severe vitamin A deficiency these membranes degenerate, scars form and the child goes blind. Vitamin A prevents all that.

Many foods can prevent xeropthalmia: milk, liverwurst, cod liver oil, spinach, or carrots. The concept of 'vitamin' extracts from these foods the relevant factor that they have in common, namely vitamin A. Food tables list the content of vitamin A and other nutrients in thousands of foods. The food table is the defining paradigm of nutrition science; it simplifies foods to a limited number of compounds that cause or prevent disease. The discovery of vitamins and other nutrients represents a triumph of reductionist science.

Scientific knowledge alone is not enough. Xeropthalmia still makes children in tropical countries go blind; poverty, ignorance, tradition and bureaucratic ineptitude prevent their receiving enough vitamin A. People in affluent countries also suffer from diseases that could be prevented by diet, such as constipation or stroke. Getting the right food to the right people requires more than scientific insight, it requires politics and campaigning. But everything begins with the knowledge of what it is in food that makes people healthy or ill. Here the reductionist approach has created knowledge that lasts.

The reductionist approach to diet and heart disease

Coffee, cholesterol and coronary heart disease

Thirty-five years ago, when I came to Wageningen University, deficiency diseases had disappeared from affluent countries and vitamins were old hat. All the buzz was about diet and coronary heart disease. I had a unique chance to apply the reductionist approach to this issue. In the early 1980s there was much discussion whether coffee raised cholesterol and caused heart disease. Cholesterol is indispensable for life, it is part of the membranes that

subdivide cells and tissues and it is the starting material for steroid hormones, bile acids and vitamin D. However, if its concentration in blood is too high it will obstruct coronary arteries and cause a heart attack in a process that takes decades.

Scandinavian scientists claimed that coffee raised blood cholesterol levels and the risk of heart disease, but Dutch and American scientists did not find this. How could coffee cause high cholesterol levels and heart attacks in one country but not in another? The key turned out to be the brewing method.[12] Finns, Swedes and Norwegians boiled ground coffee with water in a pan, while the rest of the world used a paper filter. There were lots of hypotheses why boiling should make coffee hypercholesterolemic. I speculated it had to do with floating coffee dregs, so I asked one of my coworkers to centrifuge some boiled coffee. There were indeed dregs at the bottom of the tube, but to our surprise, there was also a thin layer of fat floating on top. Evidently there were fat globules in boiled coffee which the floated to the surface during centrifugation.

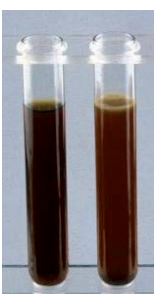


Figure 2. Filtered and boiled coffee after centrifugation. Note the fat floating on the boiled coffee (right).

When I saw that sliver of fat, my chemist's heart beat faster. There had to be a special molecule in there, and I was going to discover it. I secured the cooperation of Nestlé Research, who knew everything about coffee, and in three years we showed that the cholesterol raising factor in coffee beans was a fat-soluble compound called cafestol. It is a major component of the oil that is a natural component of coffee beans. Hot water extracts some of the oil, including the cafestol, from ground beans into the coffee brew if you do not interpose a filter.

The coffee industry used the new knowledge to make instant coffee free from cafestol, and Scandinavians switched to filter coffee. They had been doing that anyway because boiled coffee was old-fashioned, but the new knowledge speeded this up. The switch in brewing practices is thought to explain one third to one half of the 10% fall in serum cholesterol in Scandinavia between 1970 and the 1990s, and to have contributed significantly to the fall in coronary mortality.[12] More recently, the developers of the Senseo coffee machine designed the coffee pads in such a way that no cafestol could get into the brew.

So the coffee mystery was reduced to one molecule. Until cafestol was identified, any new coffee brew would need to be fed to dozens of volunteers for four weeks to know if it raised cholesterol or not. There are many types of beans and many ways to brew coffee. Now it was enough to analyze the cafestol content.

Trans fatty acids and HDL

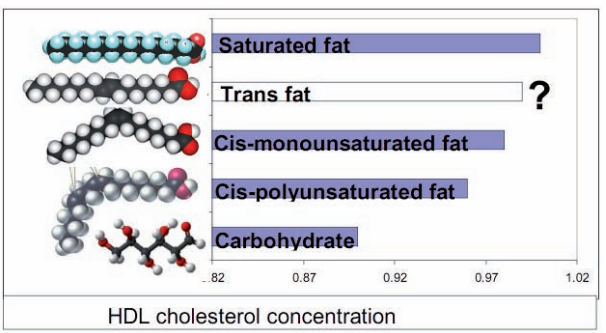


Figure 3. Katan's hypothesis: straight fatty acids cause higher HDL, so trans should cause higher HDL than cis

The coffee factor was fun and not unimportant, but the core business of diet and coronary heart disease research was fats and cholesterol. Saturated fats raised and polyunsaturated fats lowered the concentration of cholesterol in blood, and replacing saturated fat from dairy and meat by polyunsaturated fat from vegetable oils had been shown to reduce the rate of heart disease in randomized clinical trials.[13] (Fats is not the correct term, the right terms are saturated and polyunsaturated fatty acids, cumbersome terms when often repeated.) However, it was dawning on scientists that not all cholesterol in blood is bad; only the cholesterol carried in LDL particles caused coronary heart disease, the cholesterol in HDL particles protected against coronary

heart disease.[14] This made it important to understand the effects of fats on HDL..

I had a theory that the curvedness of fatty acids determined their effect on HDL: the more curved the fatty acid, the more it lowered HDL. I wanted to do an experiment with trans fatty acids to prove my point. Trans fatty acids were almost but not quite straight, and they should therefore raise HDL in comparison with cis-unsaturated fatty acids, which are bent (figure 3). Trans fatty acids were made by partial hydrogenation of vegetable or fish oils to produce hard fats. Such fats had been used widely in foods for a century.

When we did the experiment, it came out all wrong. The trans fatty acids not only raised LDL, but they lowered HDL more than any other fatty acid known (figure 4). I hesitated to believe this. No adverse health effects of trans fatty acids had been reported before, and in the US they were considered a healthy replacement for saturated fat. But the Editor-in-Chief of the New England Journal of Medicine did not share my hesitations, and he suggested that we state in our paper: '*The effect of trans fatty acids on the serum lipoprotein profile is at least as unfavorable as that of the cholesterol-raising saturated fatty acids*'.[15]

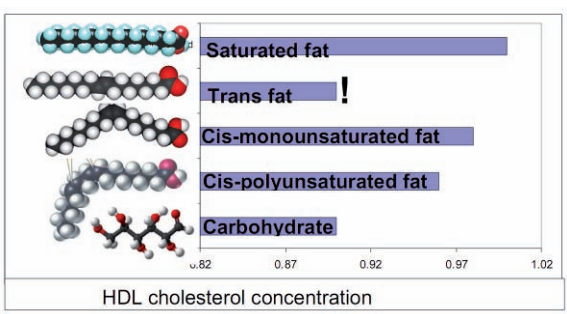


Figure 4. Katan's hypothesis refuted: trans fat caused the lowest HDL of all [15,16]

He turned out to be right. We confirmed it with a different type of trans fatty acid, and then colleagues worldwide found the same effect for all kinds of trans fatty acids. Our recent experiment[17] and quantitative review[18] suggest that the natural trans fatty acids produced by bacterial hydrogenation in the rumen of cows and sheep also lower HDL and raise LDL.

So trans fat represents another success of reductionist science. Whether you take hardened fish oil, hardened soybean oil, capsules of conjugated linoleic

acid (CLA), sheep fat, or milk fat, as soon as they contain a double bond where one hydrogen atom points one way and the next hydrogen atom the other way that fatty acid will increase LDL and decrease HDL levels. But I still do not understand why. So my Challenge # 1 to young nutrition scientists is:

#1: why do trans fatty acids raise LDL and decrease HDL?

I would not study this in laboratory animals, their blood cholesterol reacts differently to diet than that in humans.[19] What might work is to synthesize different fatty acid analogues and feed them to volunteers. Do not think it cannot be done in humans. Some people said we could never purify the cholesterol raising factor from coffee using trials in humans, but we did.

If you are at it you might as well tackle Challenge # 2:

#2: why do saturated fatty acids increase LDL, and polyunsaturated fatty acids lower it?

This question has been studied fruitlessly for 60 years, so do not expect this one to be easy!

For the diehards I have an even harder challenge,

 # 3: do diets that raise HDL reduce heart attacks?

We still do not know if high HDL levels in blood actively protect arteries, or are merely a sign of something else. (cf. figure 7) Testing this question with diets is tough. One option is to keep 50 000 poor people in China on a rice diet for 5 years and give another 50 000 people large amounts of olive oil to raise their HDL. You could add two alcoholic drinks per day to raise HDL even more. But it is not easy, and the alcohol is ethically questionable. Drug studies might give the answer sooner.

Beyond science: elimination of trans fatty acids from foods

Although the scientific facts about trans fatty acids were clear, they were resisted by powerful industrial interests and by scientists who had thought and stated throughout their careers that trans fatty acids were innocuous. The tipping point came when Prof. Walter Willett and coworkers from Harvard University found that trans fat intake was associated with risk of heart disease in US nurses. They stated that trans fatty acids were causing 30 000 deaths from heart disease per year in the USA alone.[20] That caused an uproar even though the number was a conservative estimate.

Unlike its US competitors, Unilever decided to get rid of trans right away. They had an edge on other companies, because they had the scientific know-how both to judge the nutritional evidence, and to change the fats in thousands of products without changing their taste or appearance. A great example of enlightened self-interest! In the USA it took another 10 years and a lot campaigning by the group at Harvard and the Center for Science in the Public Interest before reduction of trans fatty acids in foods started in earnest. The change in Europe was speeded up when Danish scientists managed to get trans fat banned in their country.[21]

The great thing was that consumers did not need to do a thing. Some fat molecules had changed their spatial configuration in food but you could not see or taste that, so everybody ate the new healthier products without complaints. This has led to 3000 to 5000 fewer cases of coronary heart disease per year in the Netherlands alone.[22] The epidemiological studies suggest even larger numbers, but I prefer the conservative estimates.[23]

The rise of food pattern science

Low-fat diets and the carbohydrate fiasco

The removal of trans fat was useful, but the major cholesterol-raising factor in food was still saturated fat. Replacing it with polyunsaturated fat lowered cholesterol, which is why in the 1960s, in the absence of effective drugs, pharmacies and hospitals in the Netherlands distributed cans of *B*lood *C*holesterol *L*owering margarine to patients with hypercholesterolemia. However, resistance to polyunsaturates was rising. Recommending polyunsaturated fatty acids benefitted the margarine industry, which made some people uneasy. There were also worries that polyunsaturated fatty acids caused cancer. We now know this was wrong [24], but in the 1970s it helped to spur a move to less fat and more carbohydrate instead of less saturated and more polyunsaturated fat. Low-fat sounded like an exciting new idea. It was thought to deal with many western diseases: it would reduce cholesterol and heart disease, but also obesity, diabetes, cancer, diverticulitis and constipation.

Unfortunately we found that low-fat high-carbohydrate diets lowered not just the bad LDL cholesterol in blood, but also the good HDL cholesterol (Figure 4).[25,26] That made the benefit of less fat and more carbohydrate questionable. One of our studies led to a headline in the Volkskrant '*Minder Vet ook niet Goed'* [*Less Fat No Good Either*]. We were embarrased, because it was not

politically correct to subvert fat reduction. I presented our findings on low-fat high-carbohydrate diets and HDL at conferences, but they were shrugged off. Low-fat ruled and I was too hesitant to go against the current. It took me 15 years and the example of Walter Willett before I found the courage to speak out firmly against high-carbohydrate diets.[27]

Meanwhile the low-fat high-carbohydrate bandwagon rolled on. 'Fat is bad' is a lot simpler than: 'polyunsaturated fatty acids are better than saturated fatty acids'. Unfortunately low-fat is also a fuzzy concept. The proponents of low-fat diets did not just mean that there should be fewer triacylglycerol molecules in foods (triacylglycerol is the chemical name for fat). Low-fat was also shorthand for a healthy food pattern: less fast food, less meat and high-fat milk products, and more whole-wheat bread, fruits, vegetables, and beans. And indeed, vegetarians were healthier than omnivores, and people from Japan, who ate lots of rice and soybeans, lived longer than people in Finland and the USA with their high-fat diets. It also seemed plausible that fat makes you fat because fat has 9 calories per gram and carbohydrate only 4. Biochemists proposed ingenious schemes why fat causes obesity and carbohydrate did not. I could see that these schemes were wrong, but I lacked the courage to say so.

Figure 5. Healthy foods (top) and less healthy foods (bottom) can both be low in fat

People in Europe and the US also had more breast and colon cancer than the Japanese, and high-fat diets could be made to produce cancer in laboratory animals. That gave the word fat a particularly ominous ring. But when the evidence finally came in it turned out that low-fat diets did not prevent obesity or cancer in humans, and their effect on heart disease was doubtful. As a result nutrition science lost a lot of credit; much of the acrimony against nutrition scientists on the internet concerns carbohydrates and low-fat diets.

The basic mistake of the low-fat hypothesis was that a label was mistaken for a cause (figure 5). People with a certain way of life and a certain food pattern had less heart disease, obesity and cancer. One aspect of that way of life was that their foods contained less fat, but it was not proven that the fat molecules themselves caused disease. The food industry brought this home; they always push the envelope to the limit. Marketers had heard that fat was bad, but they were not going to promote beans, because their customers did not want beans. Instead, they created low-fat cookies and low-fat chips, and they labeled soda drinks as 'cholesterol- and fat-free'. I do not blame them, they followed the science. Americans gorged on carbohydrates (figure 6), and obesity hit an all-time high.

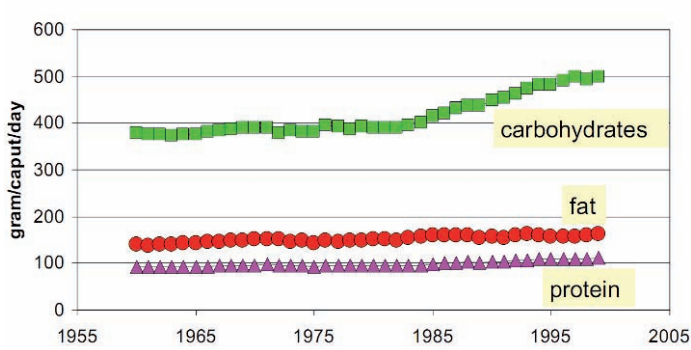


Figure 6. The increase in carbohydrate intake the USA led to increased intake of calories (www.cnpp.usda.gov)

The carbohydrate fiasco was due to a shift of emphasis in research from nutrients to food patterns. Unfortunately, that did not stop the rise of food pattern science.

Randomized trials deflate a nutrition boom

Paradoxically, food pattern science was also spurred on by the failure of randomized controlled trials to show benefits of vitamin supplements.

Starting in the 1980s, observational epidemiological studies had found many new relations between foods and health. Some of these were thought to be due to 'bioactive' compounds in foods such as polyphenols, phyto-estrogens and glucosinolates. Others were ascribed to known vitamins and minerals, but in higher doses than the tiny amounts needed to prevent deficiency

diseases. These new findings called out for testing in randomized clinical trials, which are the gold standard for proving that something cures or prevents disease. These trials started to report their findings in the 1990s, and the outcomes were disappointing.

The first molecule to fail was a form of vitamin A called beta-carotene. High intakes of beta-carotene were thought to explain why people who eat vegetables have less risk of getting cancer. But in controlled trials pure beta-carotene, when given to volunteers with a high risk of cancer, actually increased cancer rates.[28] And the amount was not all that high: theoretically, a daily glass of carrot juice contains enough beta-carotene to raise cancer risk in smokers by 20-30%.

Beta-carotene was thought to be an antioxidant, and by the 1990s antioxidants had become the new panacea. Vitamin E is the archetypical antioxidant. It was thought to prevent damage to LDL, the carrier of cholesterol in the blood. Damaged LDL was thought to depose its cholesterol in the walls of arteries, like wrecked trucks spilling their cargo by the side of the road. Vitamin E would prevent that, and in that way prevent heart disease. That was a fascinating hypothesis, but long before it had been properly tested, food and supplement companies started touting antioxidants in their products. The functional food and supplement business boomed.

But when the randomized controlled trials on vitamin E were finally completed, they showed no evidence that it protected against heart disease or cancer. The same happened with B-vitamins and homocysteine. Homocysteine is a protein metabolite. People with high levels of homocysteine in their blood have an increased risk of stroke and heart disease, and folic acid and other B-vitamins lower blood homocysteine concentrations. However, in randomized trials these vitamins did not reduce stroke or heart disease. So homocysteine is a sign of increased risk, like a red light on a car's dashboard, but not a cause (figure 7). Similarly, the mineral selenium failed to prevent prostate cancer in a randomized controlled experiment. The jury is still out on fish oil, and there is a new star in the form of vitamin D, but by and large the randomized trials suggested that nutrition had overreached itself.

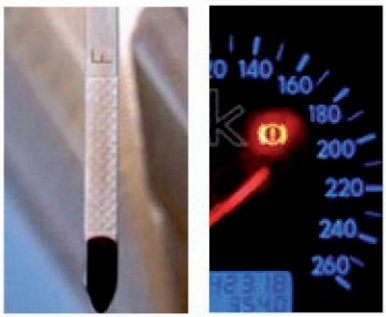


Figure 7. A low oil level (left) is a cause of engine failure, but a red light (right) is meremly a sign, and turning off the light will not save the engine

The failure of vitamins to prevent disease showed up weaknesses in the scientific disciplines that had suggested benefit. The basic sciences had extrapolated too much from cells and animal models to humans; the animals turned out to be no models of the effect of foods on disease in humans.

Epidemiological studies have a different weakness. Advances in nutrition often start by observing what people eat and whether they stay healthy or become ill. That is called observational epidemiology, or epidemiology for short. Epidemiology is crucial, it yields the ideas that bring medicine in general and nutrition in particular forward. But the very triumphs of preventive medicine make further epidemiological research harder to do. The problem is that many educated people do a lot to stay healthy. They do not smoke, they exercise, they keep their body weight, cholesterol and blood pressure down, they eat lots of fruits, vegetables, fish, vitamin supplements, and antioxidants, and drink lots of water and two glasses of red wine per day. They do stay healthier, so they do something right. But which part of their healthy living package works and which part is superfluous? These same people listen to classical music, but Bach does not prevent heart disease. Do fish and vegetables prevent heart disease, or is smoking, cholesterol and blood pressure the whole story?

Figure 8. People with low socioeconomic status (above, left) have less healthy lifestyles, and their musical preferences also differ from people with a high socioeconomic status (below).

All the components of the healthy lifestyle are entangled, or as the epidemiologists say, confounded with each other. Epidemiologists use mathematics to estimate the contribution of each separate lifestyle factor, but mathematical untangling sometimes does not work. There is residual confounding, and there is also unmeasured confounding by factors that have not been assessed.[29] For instance, healthy people might be better at selecting the right doctor, asking him the right questions and following his advice.

The beta-carotene story is a case in point. There is more lung cancer among smokers with a low than with a high intake of beta-carotene from vegetables. But the reason is probably that smokers who dislike vegetables smoke more cigarettes per day [30]. Epidemiological techniques are too imprecise to pick that up. So I think that the unfavorable results of the trials are correct, and that the epidemiology may have been wrong.

We urgently need to investigate the impact of residual and unmeasured confounding in nutritional epidemiology. I have tried to get around this problem by using genetics, in an approach that was later labeled Mendelian Randomization.[31-33] But Mendelian Randomization is not enough.

Hence my next challenge is:

#4: is confounding eliminated by adjusting for confounders?

We need a tool to estimate residual and unmeasured confounding per study. One way is to measure something that is associated with a healthy lifestyle but cannot be causal by itself, for instance musical preference (figures 8 and 9), and calculating the relative risk associated with it. Any relative risk that deviates from 1 after multivariate adjustment would point to the existence of residual or unmeasured confounders. Taking up this challenge might not be a great career move, because the results could put into question current epidemiologic practice. So perhaps it should be done by someone whose career is completed, or has yet to start.

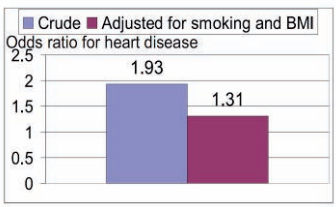


Figure 9. Risk for heart disease of listening to music popular with people of low socio-economic status. If musical preference correlates with smoking and BMI (r=0.5), and both are measured imprecisely, residual confounding will cause an apparent association of heart disease with musical preference even after statistical correction. Simulated using data from reference[29]

Food patterns as a backlash from the randomized trials

Paradoxically, the outcomes of the randomized trials led to increased fuzziness in nutrition research. The idea that the remarkable effects produced by 25 years of epidemiology might all come to nothing, and that beta-carotene caused cancer, was hard to swallow. Instead, many scientists insisted that the benefits seen in epidemiology must be real. The fact that single nutrients failed to work in trials only showed that large amounts of single nutrients may not have the same effect as the combination of small amounts of many nutrients found in foods. Beta-carotene-rich vegetables were still thought to prevent cancer because they contain a complicated mix of natural substances that cannot be mimicked by synthetic beta-carotene pills.

I am not convinced by the synthetic versus natural argument. Synthetic beta-carotene and beta-carotene from vegetables are the same substance in a different package, like bottled and tap water. I am also not convinced by the combination argument; there is no evidence that food components have vastly different effects when they are combined than when they are separate. It is an untestable hypothesis and rests on belief. Still, it convinced many scientists that we should not study nutrients but food patterns.

A food pattern is what a certain group of people eats. The best studied food pattern is the Mediterranean diet. It was eaten in Crete and southern Italy in the 1960s, and its intake was associated with low rates of cardiovascular disease, obesity, diabetes and various cancers. That same association is now seen in affluent western countries: Americans who eat olive oil, vegetables, fruits, whole-wheat bread and who drink a few glasses of red wine per day are healthier than their compatriots who live on hamburgers and coca cola. However, Americans who dip their bread in olive oil differ from their compatriots in many other ways.

There is one argument about food patterns that I do find appealing: they might be useful in nutrition education. Food patterns can be used to steer people away from highly processed foods with lots of calories. Big Macs and coca cola do not fit into the Mediterranean or Paleolithic food pattern, and someone who eats like Cretans in 1960 will not easily get fat, because the food is hard to chew and has a lot of bitter leaves (figure 10).

Figure 10. Cretan lunch served to the author during field work in 1985. Note the olive oil. The wild greens (center) were picked by the lady of the house from a hillside right before lunch.

But people do not want bitter foods that are hard to chew, and food companies know that. Twenty years ago industry invented low-fat foods for people to gorge on, and I think they can do the same for Mediterranean foods because the concept of ‘Mediterranean’ leaves marketers plenty of room. Potatoes are a vegetable, so french fries fried in olive oil might pass as Mediterranean. Eating fruits can be messy and time consuming, and they do

not always taste great, so can we replace them with a shake from a bottle? And foods high in fiber are hard to chew, so why not use inulin, a sugar that legally counts as fiber?

Even olive oil is not assured its place in the Mediterranean diet, as shown by the Lyon diet heart study, the one randomized trial that showed heart disease was reduced by a Mediterranean diet.[34,35] The diet in this study was called Cretan Mediterranean, but it contained rapeseed oil which had 8 times as much plant omega-3 fatty acids (i.e. alpha-linolenic acid) as olive oil. The authors ascribed much of the remarkable outcome of their study to this high intake of alpha-linolenic acid. Olive oil is deficient in omega-3 fatty acids. Does that mean Mediterranean diets are better without olive oil?

Why food patterns are not good science

Food patterns are easy to subvert because they do not meet the basic requirements of science. Science reduces many different things to one thing that is measurable and immutable, and that one thing can then be applied widely. Science simplifies planets, airplanes and electrons to masses, and the properties of masses hold for everything that moves. Apple trees, flowers and algae all grow because chloroplasts use sunlight to make fuel. Apple trees also stand for nature, nostalgia, and memories of youth, but when I want to understand growth I focus on chloroplasts. As Lord Kelvin said: '*When you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind'.* Food pattern science provides knowledge of a meagre and unsatisfactory kind. Our definition of 'healthy' must not be based on elastic concepts like 'Mediterranean' but on identification and measurement of the compounds responsible for benefit.

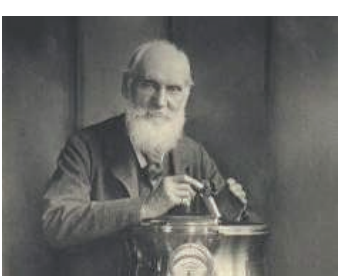


Figure 11. Lord Kelvin

There are lessons from the past that speak to this. Two hundred and fifty years ago James Lind compared the effects of lemon juice and vinegar on scurvy.[36] Both are clear fluids with a similar taste, and they can be used interchangeably on salads. But lemon juice cured scurvy and vinegar did not. Lemon juice becomes inactive if it is cooked, or if it is stored in copper pots. Those effects, and the effect of any food or supplement on scurvy, can be reduced to the presence or absence of vitamin C. What tastes good on salads is a poor guide to what will cure scurvy.

Foods in need of a reductionist approach

There are plenty of examples how food patterns need to be replaced by something that can be measured and expressed in numbers.

Whole grains are thought to reduce the risk of coronary heart disease, so all kinds of high-fiber foods claim this benefit because fiber seems like the essence of wholegrain. However, wheat bran does not lower blood cholesterol but raises it.[37,38] People who eat a fiber-rich diet have less coronary heart disease, but is it the fiber, or something else in wheat, or some other healthy things that they do?

Eating vegetables lowers blood pressure,[39] but there is vegetables and vegetables. Vegetables contain variable concentrations of nitrate, and nitrate could contribute to the lowering of blood pressure. If that is indeed the case then organically grown vegetables will be less effective because they contain less nitrate. Here is a challenge I have uttered before:

#5: do vegetables lower blood pressure because of nitrate?

This requires an experiment in volunteers fed organic and conventional vegetables for a month or so. Since I first offered the idea two years ago[40] several new papers on this topic have appeared, but a study with actual foods has still not been done.

Figure 12. Glasshouse with lettuce. Dutch glasshouse vegetables are high in nitrate

It would be a setback for organic farming if nitrate turns out to be the key to the beneficial effect of vegetables on blood pressure. On the other hand, meat from organically reared animals might be healthier than conventional meat. Conventional pig and chicken breeders in the Netherlands use huge amounts of antibiotics to fight disease in their animals and make them grow faster.[41] Those antibiotics cause the emergence of antibiotic-resistant bacteria, which jump from the animals to the farmers. So when a hog farmer goes into hospital he is isolated as if he harbors a dangerous infection. The Extended Spectrum Beta Lactamase or ESBL bacteria are especially feared.[42] Could consumers get ESBL infections from chicken meat directly instead of being infected through chicken breeders? That can be determined by comparing people who eat chicken with those who do not. Therefore my challenge is:

#6: do vegetarians have fewer ESBL bacteria in their gut than omnivores?

All this takes is to recruit a few hundred vegetarians and matched controls, have them swipe their anus with a swab, and send the swabs to the laboratory. If that shows that meat can contaminate its consumers directly, the next step is to test conventional versus organic meat. That is a bit harder but still doable, and it would be of great medical and social significance.

Obesity

The problem with weight loss trials

People become obese when they eat more calories than they expend. Classical nutrition science appears helpless in tackling this seemingly simple problem. High-carbohydrate diets have failed to produce substantial long-

term weight loss, but low carbohydrate, high-fat diets have done no better, and whether high-protein diets will help remains to be seen.

The reason for the perplexing outcomes of weight loss trials is that they look like trials of the effect of nutrients on metabolism, but in fact they are experiments in human behavior. Weight loss occurs only if calorie intake is decreased by eating less, or calorie expenditure is increased by moving more. In the short term, all diets can achieve that. No matter whether the diet is high in fat, low in fat, high in plant foods or high in meat, most subjects lose weight. This is best explained by lack of blinding: subjects know that the diet is testing their ability to lose weight. When people know that they are supposed to lose weight they may adjust their food intake and activities accordingly. Second, the diet may be less tasty, convenient or familiar than the habitual diet. That hinders food intake. The reason why people lose weight on a new diet may simply be that it smells unfamiliar or is harder to chew.

The need for blinding is much more pressing in obesity research than in pharmaceutical trials. If we think that certain food components are more fattening than others, the least we can do is to compare them with an placebo that looks, smells and tastes the same. Otherwise any effect on body weight may be caused by the taste, appearance and appeal of the food, and not by specific molecules in it. Designing the placebo treatment also confronts the researcher with the need to specify his hypothesis: what exactly is the food property or component that is supposed to cause weight loss?

Figure 13. Cans of sugary or sugar-free lemonade used in the Drink study

That is why we are doing the Drink study. This study recruited children who were used to have a sugar-containing drink every day at school during the morning break. They were randomized to receive a control drink with sugar, or an indistinguishable test drink without sugar, for 18 months (figure 13). The hypothesis tested is that the human body does not detect calories in the form of liquid sugar. As a consequence, surreptitious removal of such

calories will not be compensated by increased intake of other foods and the child will become leaner. There are epidemiological studies and experiments on satiation supporting this hypothesis, but there are no double-blind experiments with body fatness as an endpoint.

We hope to report the outcome of this study in 2012, but scientific questions are rarely settled by a single experiment. Hence my final challenge to you is:

#7: do liquid carbohydrates cause weight gain if no one knows who gets sugar and who does not?

This is a nutrient-based approach to obesity; the nutrient consists of sugar surrounded by water molecules. But the nutrient-based approach will not solve the obesity problem.

Obesity is not caused by food composition

Liquid calories are an interesting hypothesis, but by and large obesity is not a problem of food composition. Take the proverbial fattening food, french fries. Nutritionally speaking there is nothing wrong with them. Potatoes are a healthy plant food, and the vegetable oil in which they are fried lowers cholesterol. If french fries are served with potassium-rich instead of regular salt they even lower blood pressure. The problem with french fries is that for €2 you can buy a portion worth 700 kcal on every street corner, they taste great, and one does not need a knife and fork to eat them. As a result, consumers overeat. But the science needed to solve that is not nutrition science but psychology and economics.

Fast food does not make people fat because of some component of the food. You can actually lose weight on a fast food diet; just mix the hamburger, french fries and coca cola in a bucket prior to consumption. The same mixing would occur in your mouth and stomach when you eat them separately. The difference is that the mash is repulsive, so you eat less. But the glycemic index, fat content, energy density and portion size are the same. It is taste and appeal rather than composition that make fast food fattening.

Food producers, supermarkets and fast food outlets make food as attractive as possible, and package it so that it is easy to keep and to carry. That meets man's age-old longing for calories to survive starvation. The solution of the obesity problem may therefore be fewer fast food outlets, higher prices for calorie-rich food, fewer cars, more bicycle paths and more room for children to play outside instead of watching TV. Within the EMGO+ institute, of which our department is a member, high-quality research is done on these

aspects of the obesity problem and many more. But that is not nutrition research as I define it; nutrition research investigates the composition of foods and what food components do to human metabolism and health. That approach fails because obesity is not a problem of food composition.

The way ahead

Nutrition is an ambitious science. The belief that you can prevent major diseases by eating differently seems far-fetched. Still, nutrition research has shown and continues to show that this can be achieved.[43] However, there are no quick fixes. Good science, like good food, requires time. It will take lots of work and money to make new discoveries, but it is worth it. Some people would never have seen their grandchildren if our food was still full of trans fatty acids, or if coffee in Finland was still full of cafestol. I do not know how many people, but even if it was one it was worth it.

People I am grateful to

I thank the Executive Board and the board of the Faculty of Earth and Life Sciences of the Vrije Universiteit. They have been generous and cordial hosts to me in the past five years. I thank the Royal Netherlands Academy of Sciences for my Academy Professorship, which set me free to do what I thought was right.

Most of all I thank those who have accompanied me on my 40-year trip through science, and I thank my family and friends, many of whom have known me for longer than that. Some colleagues whom I cherished are no longer with us, but fortunately most are still alive and in good health. It means a lot to me that so many of you are in the audience today. Thank you for teaching me, for your criticisms, your integrity, your long days and nights at work, for your confidence in me when I was not confident myself, and also for your funding, because it meant you had trust in me.

I have been blessed in my work beyond expectation, and I am grateful that I could celebrate that with you today.

Katan's challenges

#1 Why do trans fatty acids raise LDL and decrease HDL?

#2 Why do saturated fatty acids increase LDL, and polyunsaturated fatty acids lower it?

#3 Do diets that raise HDL reduce heart attacks?

#4 Is confounding eliminated by adjusting for confounders?

#5 Do vegetables lower blood pressure because of nitrate?

#6 Do vegetarians have fewer ESBL bacteria in their gut than omnivores?

#7 Do liquid carbohydrates cause weight gain if no one knows who gets sugar and who does not?

References

1. Michael Pollan. *In Defense of Food. Introduction.*. New York, USA: Pinguin Books; 2008.

2. Lawlor DA, Davey Smith G, Kundu D, Bruckdorfer KR, Ebrahim S. Those confounded vitamins: what can we learn from the differences between observational versus randomised trial evidence? *Lancet*. 2004;363(9422):1724-1727.

3. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. *PLoS Med*. 2008;5(3):e67.

4. Katan MB, Giling LJ, Van Voorst JDW. pH dependence of the transient absorptions in the flash photolysis of 3-methyllumiflavin. *Biochim Biophys Acta*. 1971;234:242-48.

5. Kraayenhof R, Katan MB. Energization of the chloroplast membrane as revealed by fluorescent probes. In: *Proceedings 2nd International Congress on Photosynthesis*. Stresa: Forti G., Ed.; 1971:937-49.

6. Haaker H, Berden JA, Kraayenhof R, Katan MB. The use of probes as indicators for energization of membranes. In: *Biochemistry and biophysics of mitochondrial membranes*. Van Dam, K. and Azzone, G.f., eds. New York: Academic Press; 1972:329-40.

7. Kraayenhof R, Katan MB, Grunwald T. The effect of temperature on energy-linked functions in chloroplasts. *FEBS Letters*. 1971;19:5-10.

8. Katan MB. Detection of cytochromes on sodium dodecylsulphate-polyacrylamide gels by their intrinsic fluorescence. *Anal Biochem*. 1976;74:132-37.

9. Katan MB. Comparative immunological and electrophoretic studies of the cytochrome bc1 complex of different organisms. In: *Genetics, biogenesis and bio-energetics of mitochondria*. Bandlow W., Editor. Berlin: de Gruyter; 1976:279-288.

10. Katan MB, Pool L, Groot GSP. The cytochrome bc1 complex of yeast mitochondria: isolation and partial characterization of the cytochrome bc1 complex and cytochrome b. *Eur J Biochem*. 1976;65:95-105.

11. Katan MB, Van Harten-Loosbroek N, Groot GSP. The cytochrome bc1 complex of yeast mitochondria: site of translation of the polypeptides in vivo. *Eur J Biochem*. 1976;70:409-17.

12. Urgert R, Katan MB. The cholesterol-raising factor from coffee beans. *Annu Rev Nutr*. 1997;17:305-24.

13. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med*. 2010;7(3):e1000252.

14. Miller GJ, Miller NE. Plasma High-Density-Lipoprotein concentration and development of ischaemic heart disease. *Lancet*. 1975;1:16.

15. Mensink RP, Katan MB. Effect of dietary trans fatty acids on high-density and low- density lipoprotein cholesterol in healthy subjects. *N Engl J Med*. 1990;323:439-45.

16. Mensink RP, Zock PL, Kester ADM, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr*. 2003;77:1146-1155.

17. Wanders AJ, Brouwer IA, Siebelink E, Katan MB. Effect of a high intake of conjugated linoleic acid on lipoprotein levels in healthy human subjects. *PLoS One*. 2010;5:e9000.

18. Brouwer IA, Wanders A, Katan MB. Effect of animal and industrial trans fatty acids on HDL and LDL-cholesterol levels in humans – a quantitative review. *Plos One*. 2010;5:e9434.

19. Van Raaij JMA, Katan MB, Hautvast JGAJ. Casein, soya protein, serum cholesterol. *Lancet*. 1979;2:958-8.

20. Willett WC, Ascherio A. Trans fatty acids: are the effects only marginal? *Am J Public Health*. 1994;84:722.

21. Stender S, Dyerberg J. [Denmark is the first county in the world to forbid the use of industrially produced fatty acids]. *Ugeskr. Laeg*. 2004;166(1-2):29-32.

22. Oomen CM, Ocké MC, Feskens EJM, et al. Association between trans fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population-based study. *Lancet*. 2001;357:746-51.

23. Katan MB. Regulation of trans fats: the gap, the Polder, and McDonald's French Fries. *Atherosclerosis*. 2006;7(2):63-6.

24. Zock PL, Katan MB. Linoleic acid intake and cancer risk. A review. *Am J Clin Nutr*. 1998;68:142-53.

25. Brussaard JH, Dallinga-Thie GM, Groot PHE, Katan MB. Effects of amount and type of dietary fat on serum lipids, lipoproteins and apoproteins in man: a controlled 8-week trial. *Atherosclerosis*. 1980;36:515-27.

26. Brussaard JH, Katan MB, Groot PHE, Havekes LM, Hautvast JGAJ. Serum lipoproteins of healthy persons fed a low fat diet or a polyunsaturated fat diet for three months: a comparison of two cholesterol-lowering diets. *Atherosclerosis*. 1982;42:205-19.

27. Katan MB, Willett WC, Grundy SM. Beyond low fat diets. *N Engl J Med*. 1997;337:563-66.

28. Omenn GS. Chemoprevention of lung cancer: the rise and demise of beta-carotene. *Annu Rev Public Health*. 1998;19:73-99.

29. Fewell Z, Davey Smith G, Sterne JAC. The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. *Am. J. Epidemiol*. 2007;166(6):646-655.

30. Stram DO, Huberman M, Wu AH. Is residual confounding a reasonable explanation for the apparent protective effects of beta-carotene found in epidemiologic studies of lung cancer in smokers? *Am. J. Epidemiol*. 2002;155(7):622-628.

31. Katan MB. Apolipoprotein E isoforms, serum cholesterol, and cancer. *Lancet*. 1986;1:507-8.

32. Keavney B. Commentary: Katan's remarkable foresight: genes and causality 18 years on. *International Journal of Epidemiology*. 2004;33(1):11 - 14.

33. Trompet S, Jukema JW, Katan MB, et al. Apolipoprotein e genotype, plasma cholesterol, and cancer: a Mendelian randomization study. *Am J Epidemiol*. 2009;170:1415-21.

34. De Lorgeril M, Renaud S, Mamelle N, et al. Mediterreanean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet*. 1994;343:1454-9.

35. Renaud S, de Lorgeril M, Delaye J, et al. Cretan Mediterranean diet for prevention of coronary heart disease. *Am J Clin Nutr*. 1995;61:1360S-1367S.

36. Lind J. *A treatise on the scurvy*. Third Edition. London: S. Crowder et al. http://books.google.nl/books?id=T1OT3tYmh5wC&printsec=frontcover&dq

=james+lind+scurvy&hl=en&ei=sQpMTb68LYiCOs6Q7AE&sa=X&oi=book_result&ct=result&resnum=1&ved=0CCUQ6AEwAA; 1772.

37. Stasse-Wolthuis M, Katan MB, Hermus RJJ, Hautvast JGAJ. Increase of serum cholesterol in man fed a bran diet. *Atherosclerosis*. 1979;34:87-91.

38. Tighe P, Duthie G, Vaughan N, et al. Effect of increased consumption of whole-grain foods on blood pressure and other cardiovascular risk markers in healthy middle-aged persons: a randomized controlled trial. *Am. J. Clin. Nutr*. 2010;92(4):733-740.

39. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med*. 1997;336:1117-24.

40. Katan MB. Nitrate in foods: harmful or healthy? *American Journal of Clinical Nutrition*. 2009;90(1):11-2.

41. Bondt N. Antibioticagebruik op melkvee-, varkens- en pluimveebedrijven in Nederland; Gebruik in 2007 in vergelijking met voorgaande jaren Den Haag, LEI, 2009, Rapport 2009-015. 2009. Available at: http://www.lei.dlo.nl/publicaties/PDF/2009/2009-015.pdf.

42. Kluytmans J, Vandenbroucke-Grauls C, Van der Meer JWM. Antibiotica-resistentie: maatregelen hoognodig. *Ned Tijdschr Geneeskd*. 2010;154:A2261.

43. Katan MB, Boekschoten MV, Connor WE, et al. Which are the greatest recent discoveries and the greatest future challenges in nutrition? *Eur J Clin Nutr*. 2009;63(1):2-10.